

REMARKS

Applicant respectfully requests reconsideration.

Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 were previously and are currently pending in this application.

No new matter has been added.

Double Patenting Rejections

Claims 1, 5-9, 12, 15-18, 22, 129, 135-137 and 139-142 are provisionally rejected as being unpatentable over claims 1, 4, 5, 9-11, 13 and 14 of copending application No. 10/300,247. As stated previously, Applicant notes the provisional rejection but defers substantive rebuttal until the cited application is allowed. MPEP 804(I)(B) states that “the merits of such a provisional rejection *can* be addressed by both the applicant and the examiner without waiting for the first patent to issue” (emphasis added). Notably, the MPEP does not require that the merits *must* be addressed in such a situation. Moreover, the MPEP also states that “the ‘provisional’ double patent rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that ‘provisional’ double patenting rejection is the only rejection remaining ...”. Id. At that point, the examiner must withdraw the provisional rejection and allow the claims. Consistent with this practice, Applicant defers substantive rebuttal of the provisional rejections until the cited co-pending application is allowed.

Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 are rejected on the grounds of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 7,488,490, in view of Craig.

The Examiner states that the rejected claims are obvious variants of the cited claims “because both claim sets encompass a method of inducing mucosal immune response.” The Examiner acknowledges that “the patent claims recite inducing an immune response and not inducing a mucosal immune response as recited in the instant claims.” However, according to the Examiner, “the application specification discloses that the immune response encompasses a mucosal immune response.” The Examiner cites page 45 of the application as filed for the ‘490 patent as

support. That page, provided herewith as Appendix A, does not “disclose that the immune response encompasses a mucosal immune response.” Applicant presumes that the Examiner is referring to the teachings on this page relating to the administration routes which include mucosal and non-mucosal routes. Nothing in this teaching, however, “discloses that the immune response encompasses a mucosal immune response,” as asserted by the Examiner.

The Examiner has incorrectly stated in the Office Action at page 7 that “the type of immune response depends on the administration route.” The Examiner provides no basis or substantiating evidence for this proposition. Based on this incorrect assumption, the Examiner concludes that “the indicated passage teaches mucosal delivery and *mucosal delivery necessarily results in mucosal immune response.*” (emphasis added) Again, the Examiner provides absolutely no basis or substantiating evidence for this conclusion. The Examiner is required to provide such evidentiary support. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420-421 (CCPA 1970). Moreover, Applicant notes that various references of record indicate otherwise. For example, in Grdic et al., an antigen-adjuvant composition induced a systemic immune response after being administered orally. (Grdic et al. Eur. J. Immunol., 29:1774-1784, 1999) In Ugozzoli et al., an antigen-adjuvant composition generated a fecal immune response after being administered intramuscularly. Significantly, Ugozzoli et al. failed to generate a mucosal immune response when another antigen-adjuvant combination was administered intranasally. (Ugozzoli et al. Immunol., 93:563-571, 1998) These references refute the Examiner’s position that “mucosal delivery necessarily results in mucosal immune response.”

The Examiner is using hindsight by applying the teachings that are found *only* in the instant application (i.e., that CpG oligonucleotides are able to induce a mucosal immune response). Nothing in the ‘490 patent teaches that a CpG oligonucleotide induces a mucosal immune response, and nothing in the ‘490 patent teaches a subject that is in need of a mucosal immune response. These claim limitations are also not obvious to one of ordinary skill in the art. The teachings of Craig do not cure the deficiencies in the ‘490 patent claims.

Finally, an obviousness rejection cannot be based on that which is unknown at the time of the invention. In re Rijckaert, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). The instant application is the first disclosure of the ability of CpG oligonucleotides to generate a mucosal

immune response when administered to a mucosal site. This activity was unknown prior to the invention. The instant claims, which recite induction of a mucosal immune response in a subject in need of a mucosal immune response, would not have been obvious to one of ordinary skill in the art at the time of the invention based on the claims of the '490 patent because it was not known, nor could it have been reasonably expected, prior to the invention that CpG oligonucleotides could induce mucosal immunity.

For at least these reasons, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §103

Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 are rejected under 35 U.S.C. §103(a) as being unpatentable over Krieg et al. (US 6,239,116) in view of each Agrawal et al. (US 6, 426,334), Briles et al. (US 6,042,838), Craig (US 6,689,757), Kincy-Cain et al. (Infect. Immun., 1996, 64:1437-1440) and Berzofsky et al. (US 6,749,856).

At the outset, Applicant notes that Berzofsky et al. (US 6,749,856) has an effective prior art date of June 12, 2000 and therefore it is not prior art. The '856 patent claims priority to an international application filed on September 11, 1998 and, as a result, its 102(e) date is the date on which its requirements under §371 were met. According to the face of the patent, this date is June 12, 2000, which is after the filing date of the instant application. The reference is therefore not prior art.

Applicant has previously addressed the rejection and the Examiner is referred to the various lengthy rebuttals of record. Here, Applicant briefly summarizes those rebuttals and addresses the outstanding issues.

First, neither Krieg et al. nor Agrawal et al. teaches a method of inducing a mucosal immune response. The Examiner incorrectly states on page 8 of the Office Action that "Krieg et al. teach a method of inducing a mucosal immune response." Krieg et al. does not provide such a teaching. The Examiner incorrectly states on page 10 of the Office Action that "Agrawal et al. teach inducing a mucosal immune response." Agrawal et al. does not provide such a teaching either. Similarly, neither Krieg et al. nor Agrawal et al. teach subjects in need of a mucosal immune response.

Second, the Examiner states that it would have been obvious to substitute the administration routes recited by Krieg et al. with those of Agrawal et al. “to achieve the predictable result of inducing mucosal immunity.” As stated above, neither reference teaches induction of mucosal immunity, and therefore such induction would not be predictable. One of ordinary skill in the art would not have a reasonable expectation that the methods of these references would induce mucosal immunity. Accordingly, there can be no predictability relating to the induction of mucosal immunity, contrary to the Examiner’s assertion. That CpG oligonucleotides are able to induce a mucosal immune response when administered to a mucosal surface was not known prior to the invention. An obviousness rejection cannot be based on that which is not known prior to the invention. In re Rijckaert, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993).

Third, citing Briles, the Examiner makes the broad statement that “the prior art teaches that intranasal administration results in mucosal immunity at remote sites.” The teaching in Briles, however, is not so broad. Briles reports that “mice can be effectively immunized by intranasal (i.n.) instillation of bacterial protein immunogens, particularly *when conjugated to or mixed with cholera toxin (CT) or its B subunit (CTB)*.” (emphasis added) (See col 8 lines 15-18.) Briles further reports that “when CTB is used as an adjuvant for i.n. immunizations, specific IgA antibodies are induced in secretions of the intestinal, respiratory, and genital tracts.” (See col 8 lines 18-21.) Accordingly, Briles is emphasizing the effects of CT and CTB. These statements cannot be reasonably interpreted as teaching that intranasal administration of any antigen with any adjuvant would result in mucosal immunity at remote sites. As evidence, Ugozzoli et al. shows that not every antigen/adjuvant combination yields such results. (Ugozzoli et al. Immunol., 93:563-571, 1998.) Ugozzoli et al. reports that, when the HSV antigen gD2 is administered intranasally with adjuvant MF59 or adjuvant Iscomatrix, mucosal immunity above that achieved with antigen alone is not detected in nasal washes (i.e., locally) or in saliva, vaginal and/or fecal washes (i.e., remotely). The results of Ugozzoli et al. refute the Examiner’s statement.

The Examiner further relies on Briles for the teaching of saponin, CT and CTB adjuvants and concludes that it would have been obvious to use such adjuvants in the methods of Krieg et al. and Agrawal et al. “to achieve the predictable result of eliciting an immune response.” As stated above, since neither Krieg et al. nor Agrawal et al. teaches induction of a mucosal immune

response, there is no basis to conclude that such a result would be predictable. It was not known prior to the invention that CpG oligonucleotides induce a mucosal immune response when administered to mucosal surfaces. The Examiner has provided no rationale for why such a result would have been predictable prior to the invention.

Fourth, the Examiner states that one of ordinary skill in the art would have known, based on the teachings of Kincy-Cain et al., that CpG oligonucleotides were mucosal adjuvants. Kincy-Cain et al. states that IL-12 can augment a mucosal immune response that arises after administration of intracellular pathogen *S. dublin*. The reference provides no data to evidence mucosal immune response induction, and instead infers mucosal immunity based on overall survival of the experimental subjects. The reference further speculates that IL-12 “most probably” exerts its effects through non-antigen-specific mechanisms including through IFN-gamma production by innate immune cells such as NK cells. Nothing in this reference evidences that IL-12 induction is necessary for mucosal immune response induction or, more importantly, that CpG oligonucleotides when administered to a mucosal surface are able to induce a mucosal immune response.

The Examiner continues to look predominately to the teachings of Kincy-Cain et al. in spite of the teachings of other references of record which show that mucosal immunity can be achieved independent of IL-12. More specifically, Applicant has brought to the Examiner’s attention a number of references that teach that IL-12 may not influence a mucosal immune response and/or that the role of IL-12 in this regard may vary depending on the route of administration. Some of these references indicate that mucosal immune responses occur even in the absence of IL-12.

Simmons et al. (J. Immunol. 2002, 168:1804-1812) reports that IL-12 knockout (IL-12p40^{-/-}) mice mount gut-associated IgA responses after infection with *C. rodentium*. (See, for example, Figure 6.) The reference further reports that only a small fraction (10-15%) of the IL-12 knockout mice died post-infection, indicating that mice are able to clear the infection independent of IL-12. The reference concludes that gut-associated IgA responses are not defective in IL-12 deficient mice.

Arulanandam et al. (Vaccine 1999, 17:252-260) states that “(T)here is little information about the influence of IL-12 on mucosal immunity.” (See page 252, second column, second paragraph.) In support of this statement, the reference indicates that others have reported that intratracheal administration of IL-12 inhibits antigen-specific IgA in bronchoalveolar lavage (citing

Yang et al. Nature Med. 1995 1:890-3) and that oral administration of IL-12 enhances serum IgG and has no effect on fecal IgA (citing Marinaro et al. J. Exp. Med. 1997 185:415-427).

Arulanandam et al. itself reports no change in lung IgA levels and suppressed fecal IgA levels in mice immunized intranasally with DNP-OVA with cholera toxin B subunit and IL-12. The reference therefore shows that presence of IL-12 at a mucosal site does not induce mucosal IgA, and it further states that "only parenteral administration of IL-12 results in enhanced faecal IgA antibody levels."

Marinaro et al. (J. Immunol. 1999, 162:114-121) documents that intranasal administration of IL-12 had no effect on mucosal secretory IgA responses to oral or nasal vaccines.

In response to the teachings of these references, the Examiner has indicated that "just because the evidence of record indicates that intranasally-administered IL-12 does not induce a mucosal antibody response, does not mean that IL-12 cannot induce a mucosal immune response." The Examiner is respectfully reminded that Briles, a reference made of record by the Examiner, clearly states that "the principal determinant of specific immunity at mucosal surfaces is secretory IgA (s-IgA) which is physiologically and functionally separate from the components of the circulatory immune system." Accordingly, it was recognized in the art that s-IgA production was a defining marker of a mucosal immune response.

The Examiner further states that, based on the teachings of Krieg et al., one would have understood that CpG oligonucleotide administered orally to a subject would induce parenteral IL-12 and this in turn would induce a mucosal immune response. Even assuming *in arguendo* that IL-12 was necessary and sufficient for inducing a mucosal immune response (although Applicant disagrees), there is no indication in Krieg et al. that orally administered CpG oligonucleotide would generate sufficient levels of IL-12 to induce a mucosal immune response. At most, Krieg et al. states that "the ability of a CpG ODN to induce IL-12 secretion is a good measure of its adjuvant potential, *especially in terms of its ability to induce a Th1 immune response, which is highly dependent on IL-12.*" (emphasis added) (See col 35 lines 51-54.) A Th1 immune response is not a mucosal immune response. However, as shown by the art of record, IL-12 is not necessary and sufficient for the induction of a mucosal immune response. Moreover, as demonstrated by Krieg et al., CpG oligonucleotides modulate the production of a number of cytokines and the activation of a

variety of cells. Given the various in vivo effects caused by CpG oligonucleotides, and given the art-recognized uncertainty as to the role of various factors in mucosal immunity induction, there was no knowledge nor any reasonable expectation by one of ordinary skill in the art that CpG oligonucleotides induce mucosal immunity when administered mucosally, prior to the instant invention.

Reconsideration and withdrawal of this rejection is respectfully requested.

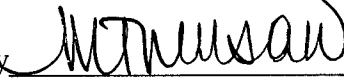
CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 23/2825 under Docket No. C1040.70006US00 from which the undersigned is authorized to draw.

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Respectfully submitted,

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administered to a subject by any mode allowing the oligonucleotide to be taken up by the appropriate target cells. "Administering" the pharmaceutical composition of the present invention may be accomplished by any means known to the skilled artisan. Preferred routes of administration include but are not limited to oral, transdermal (e.g. via a patch), parenteral injection (subcutaneous, intradermal, intravenous, parenteral, intraperitoneal, intrathecal, etc.), or mucosal intranasal, intratracheal, inhalation, and intrarectal, intravaginal etc). An injection may be in a bolus or a continuous infusion.

For example the pharmaceutical compositions according to the invention are often administered by intramuscular or intradermal injection, or other parenteral means, or by biolistic "gene-gun" application to the epidermis. They may also be administered by intranasal application, inhalation, topically, intravenously, orally, or as implants, and even rectal or vaginal use is possible. Suitable liquid or solid pharmaceutical preparation forms are, for example, aqueous or saline solutions for injection or inhalation, microencapsulated, encochleated, coated onto microscopic gold particles, contained in liposomes, nebulized, aerosols, pellets for implantation into the skin, or dried onto a sharp object to be scratched into the skin. The pharmaceutical compositions also include granules, powders, tablets, coated tablets, (micro)capsules, suppositories, syrups, emulsions, suspensions, creams, drops or preparations with protracted release of active compounds, in whose preparation excipients and additives and/or auxiliaries such as disintegrants, binders, coating agents, swelling agents, lubricants, flavorings, sweeteners or solubilizers are customarily used as described above. The pharmaceutical compositions are suitable for use in a variety of drug delivery systems. For a brief review of present methods for drug delivery, see Langer, *Science* 249:1527-1533, 1990, which is incorporated herein by reference.

The pharmaceutical compositions are preferably prepared and administered in dose units. Liquid dose units are vials or ampoules for injection or other parenteral administration. Solid dose units are tablets, capsules and suppositories. For treatment of a patient, depending on activity of the compound, manner of administration, purpose of the immunization (i.e., prophylactic or therapeutic), nature and severity of the disorder, age and body weight of the patient, different doses may be necessary. The administration of a given dose can be carried out both by single administration in the form of an individual dose unit or else several smaller dose units. Multiple administration of doses at specific intervals of weeks or months apart is